

REMARKS

Applicants respectfully request entry of the above amendments to the drawings, specification, and claims, which place the application and claims in condition for allowance or in better form for consideration on appeal, and do not require a new search by the Examiner. Figure 1 has been corrected, as required in the Notice of Draftsperson's Patent Drawing Review, so that each page of Figure 1 is labeled (e.g., as Figure 1A and Figure 1B), and the specification has been amended to reflect this correction. No new matter is added by way of the correction to the drawings or the specification.

The amendment to claim 1 finds support in the specification, for example, at page 6, lines 13-14, and elsewhere in the specification and claims as originally filed. No new matter is added by way of the amendments. Claims 1-3, 5-14, 23-31, and 37-45 were pending in the application. With entry of the requested amendment, claims 1-3, 5-7, 9-11, and 23-27 are pending.

Solely to expedite prosecution of the pending application to issue, claim 1 has been amended to refer to *in vitro* application; claims referring to *in vivo* administration have been canceled by the amendment. Thus, with the amendment, all claims refer to methods for at least partially inhibiting excessive proliferation or migration of smooth muscle cells *in vitro*.

Claims 1-3, 5-14, 23-31 and 37-45 stand rejected under 35 USC § 112, first paragraph, as allegedly not enabling; claims 1-3, 5-14, 23-31 and 37-45 stand rejected under 35 USC § 103(a) as allegedly obvious over US Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681 and further in view of a known fact. The drawings stand objected to as failing to comply with 27 C.F.R. § 1.84.

Applicants respectfully traverse the rejections.

The Objections to the Drawings:

The Draftsperson noted that the numbering of the Figures is not consecutive, and must be corrected. With this Amendment, applicants provide amended drawings in which both pages of Figure 1 are labeled consecutively as Figure 1A and Figure 1B. Accordingly, applicants believe the objections to the drawings to be overcome.

The Rejections under. § 112 ¶1

Claims 1-3, 5-14, 23-31 and 37-45 were rejected under 35 USC § 112, first paragraph, as allegedly not enabling. However, applicants respectfully note that the Examiner states that claims 1-3, 5-14, 23-31 and 37-45 are “enabling for a method of partially inhibiting proliferation or migration of smooth muscle cells in cell culture, comprising administering an effective amount of an antibody to native ErbB4 receptor” (page 3, paragraph 4, lines 2-5 of the paragraph). Applicants respectfully note that claim 1 has been amended to recite a “method for at least partially inhibiting proliferation or migration of smooth muscle cells *in vitro* comprising treating said smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2.”

Accordingly, applicants respectfully submit that the rejection to claims 1-3, 5-14, 23-31 and 37-45 under 35 USC § 112, first paragraph, as allegedly not enabling is overcome.

The Rejections under U.S.C. § 103(a)

Claims 1-3, 5-14, 23-31 and 37-45 were rejected under 35 USC § 103(a) as obvious over US Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681 and further in view of a known fact.

Applicants respectfully submit that the pending claims are not obvious over the cited combination of references.

In order to establish a *prima facie* case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In *re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that motivation or suggestion to combine the references is lacking, that there would be no reasonable expectation of success based on these references, and that the references cited by the Examiner fail to provide all the elements of the claimed invention.

Krymskaya et al. is presented by the Examiner to show the presence of ErbB4 receptors on human airway smooth muscle cells; WO 99/02681 is presented by the Examiner to show that ErbB4 receptors are present on smooth muscle cells, and that blocking signal transduction pathway mediated through this receptor can effect mitotic activity in cells expressing these receptors; and the known fact disclosed in the specification at page 5, lines 7-25 is that excessive proliferation of smooth muscle cells is involved with vascular stenosis, restenosis, and hypertension and regulation of proliferation of such cells has potential significance in treating these pathologies. Applicants respectfully note that the present claims, as amended, are directed to at least partial inhibition of proliferation or migration of smooth muscle cells *in vitro*; applicants respectfully submit that considerations of *in vivo* effects are thus moot.

Moreover, even if combined, the cited references fail to make obvious the claimed invention. None of the cited references discuss or suggest an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2. None of the cited references discuss or suggest a method for at least partially inhibiting proliferation or migration of smooth muscle cells *in vitro* by treating smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2. In addition, the cited references lack any teaching that antagonists to ErbB4 receptors would be effective to reduce smooth muscle proliferation (Krymskaya et al. teach that ErbB4 receptors are inactive, WO 99/02681 contains no disclosure regarding antagonizing ErbB4 receptors to reduce smooth muscle cell proliferation). Accordingly, whether taken alone or taken together, these references lack at least these elements of the claimed invention, and so fail to make it obvious.

As discussed in the previous response, applicants respectfully disagree with the Examiner's suggestion that Krymskaya et al. suggest that the ErbB4 receptor plays "a pivotal role in the regulation of smooth muscle cells ..." Applicants respectfully direct the Examiner's attention to Krymskaya et al., page L252, column 2, lines 7-9: "Although all EGFR family members are expressed in quiescent HASM [human airway smooth muscle] cells, ErbB-3 and ErbB-4 are functionally inactive." Applicants further note page L248, column 2, lines 37-39: "ErbB-3 and ErbB-4 in EGF-stimulated cells did not appear to be activated." Thus, Krymskaya et al. teach that ErbB4 receptors do NOT play a role in smooth muscle cell proliferation of human airway smooth muscle cells. Krymskaya et al. thus teach that interaction with an ErbB-4 receptor would be ineffective at affecting smooth muscle cell proliferation, teaching away from the claimed invention.

Teaching that ErbB-4 receptors are functionally inactive on the smooth muscle cells investigated, Krymskaya et al. does not provide any motivation to combine with any other reference to control or inhibit smooth muscle cell proliferation, or affect stenosis or restenosis, by treatment with an antagonist to an ErbB4 receptor. Whether

taken alone, or in combination with other references, Krymskaya et al. thus provides no teaching that one could control or inhibit smooth muscle cell proliferation, by treatment with an antagonist to an ErbB4 receptor.

In addition, WO 99/02681 nowhere suggests that antagonists to ErbB4 receptors might be useful to control smooth muscle proliferation. Accordingly, WO 99/02681 provides no teaching that would render obvious the claimed invention, nor any suggestion that it be combined with other references to provide the claimed invention.

“Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight.” In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Applicants respectfully submit that WO 99/02681 provides no suggestion or motivation to combine with any other reference or with knowledge available to one of ordinary skill in the art to provide ErbB-4 antagonists to control or inhibit smooth muscle cell proliferation, and that its use in a combination of references to provide such a teaching must be the result of impermissible hindsight.

Accordingly, the cited references failing to provide all the elements of the claimed invention, failing to suggest or provide motivation to provide such elements, Applicants respectfully submit that the rejections of claims 1-3, 4-14, 22-31 and 36-45 under 35 U.S.C. § 103(a) are overcome.

CONCLUSIONS

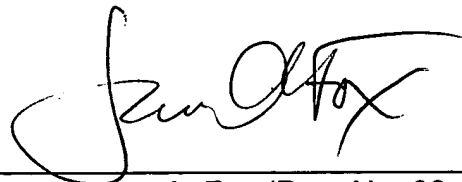
Applicants believe all rejections to be overcome as discussed above, and respectfully request the entry of the amendments, reconsideration and allowance of all pending claims. All claims being believed to be in *prima facie* condition for allowance, an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing attorney's docket no. **39766-0072 A2**.

Respectfully submitted,

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By: _____



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FIGURE 1A

1	aattgtcagc	acgggatctg	agacttccaa	aaaatgaagc	cggcgacagg	actttgggtc
61	tgggtgagcc	ttctcgtggc	ggcggggacc	gtccagccca	gcgattctca	gtcagtgtgt
121	gcaggaacgg	agaataaact	gagctctctc	tctgacctgg	aacagcagta	ccgagccttg
181	cgcaagtact	atgaaaactg	tgaggttgct	atgggcaacc	tggagataac	cagcattgag
241	cacaaccggg	acctctcctt	cctgcggtct	gttcgagaag	tcacaggcta	cgtgttagtg
301	gctcttaatc	agtttcgtta	cctgcctctg	gagaattttac	gcattattcg	tgggacaaaa
361	ctttatgagg	atcgatatgc	cttggcaata	tttttaaact	acagaaaaga	tggaaacttt
421	ggacttcaag	aacttggttt	aaagaacttg	acagaaatcc	taaatggtgg	agtctatgta
481	gaccagaaca	aattcctttg	ttatgcagac	accattcatt	ggcaagatat	tgttcggaac
541	ccatggcctt	ccaacttgac	tcttgtgtca	acaaatggta	gttcaggatg	tggacgttgc
601	cataagtcct	gtactggccg	ttgtctggga	cccacagaaa	atcattgcca	gactttgaca
661	aggacgggtg	gtgcagaaca	atgtgacggc	agatgctacg	gaccttacgt	cagtgtactgc
721	tgccatcgag	aatgtgctgg	aggctgctca	ggacctaaag	acacagactg	ctttgcctgc
781	atgaatttca	atgacagtgg	agcatgtgtt	actcagtgtc	cccaaacctt	tgtctacaat
841	ccaaccacct	ttcaactgga	gcacaatttc	aatgcaaagt	acacatatgg	agcattctgt
901	gtcaagaaat	gtccacataa	ctttgtggta	gattccagtt	cttgtgtgcg	tgcctgcoct
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1021	tgcccaaaaag	cttgtgatgg	cattggcaca	ggactattga	tgtcagctca	gactgtggat
1081	tccagtaaca	ttgacaaaat	cataaactgt	accaagatca	atgggaattt	gatctttcta
1141	gtcactggta	ttcatgggga	cccttacaat	gcaattgaag	ccatagaccc	agagaaactg
1201	aacgtctttc	ggacagtcag	agagataaca	ggtttctctga	acatacagtc	atggccacca
1261	aacatgactg	acttcagtgt	tttttctaac	ctggtgacca	ttgggtggaag	agtactctat
1321	agtggcctgt	ccttgcttat	cctcaagcaa	cagggcatca	cctctctaca	gttccagtc
1381	ctgaaggaaa	tcagcgcagg	aaacatctat	attactgaca	acagcaacct	gtgttattat
1441	cataccatta	actggacaac	actcttcagc	acaatcaacc	agagaatagt	aatccgggac
1501	aacagaaaag	ctgaaaattg	tactgctgaa	ggaatgggtg	gcaaccatct	gtgttccagt
1561	gatggctgtg	ggggacctgg	gccagaccac	tgtctgtcgt	gtcgcgctt	cagtagagga
1621	aggatctgca	tagagtcttg	taacctctat	gatggtgaat	ttcgggagtt	tgagaattgc
1681	tccatctgtg	tggagtgtga	cccccagttg	gagaagatgg	aagatggcct	cctcacatgc
1741	catggaccgg	gtcctgacaa	ctgtacaaaag	tgctctcatt	ttaaagatgg	cccaaactgt
1801	gtggaaaaat	gtccagatgg	cttacagggg	gcaaacagtt	tcattttcaa	gtatgctgat
1861	ccagatcggg	agtgccaccc	atgccatcca	aactgcaccc	aaggggtgtaa	cgggtccact
1921	agtcatgact	gcatttacta	cccattggacg	ggccattcca	ctttaccaca	acatgctaga
1981	actcccccta	ttgcagctgg	agtaattggg	gggctcttca	ttctgggtcat	tgtgggtctg
2041	acatttgctg	tttatgttag	aaggaaagagc	atcaaaaaga	aaagagcctt	gagaagattc
2101	ttggaaaacag	agttgggtgga	accattaaat	cccagtggca	cagcacccaa	tcaagctcaa
2161	cttcgtattt	tgaagaagaa	tgagctgaag	agggtaaaag	tccttggttc	aggtgctttt
2221	ggaacgggtt	ataaagggtat	ttgggtacct	gaaggagaaa	ctgtgaagat	tcctgtggct
2281	attaagattc	ttaatgagac	aactgggtccc	aaggcaaatg	tggagttcat	ggatgaagct
2341	ctgatcatgg	caagtatgga	tcattccacac	ctagtccggt	tgctgggtgt	gtgtctgagc
2401	ccaaccatcc	agctgggttac	tcaacttatg	ccccatggct	gcctgttgga	gtatgtccac
2461	gagcacaagg	ataacattgg	atcacaaactg	ctgcttaact	ggtgtgtcca	gatagctaag
2521	ggaatgatgt	acctggaaga	aagacgactc	gttcacgagg	atttggcagc	ccgtaatgtc
2581	ttagtgaat	ctccaaacca	tgtgaaaatc	acagattttg	ggctagccag	actcttgga
2641	ggagatgaaa	aagagtacaa	tgctgatgga	ggaaagatgc	caattaaatg	gatggctctg
2701	gagtgatata	attacaggaa	attcacccat	cagagtgcg	tttgagcta	tggagttact
2761	atatgggaac	tgatgacctt	tggaggaaaa	ccctatgatg	gaattccaac	gcgagaaatc
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2881	tacatggtca	tgggtcaaatg	ttggatgatt	gatgctgaca	gtagacctaa	atttaaggaa
2941	ctggctgctg	agttttcaag	gatggctcga	gacctcaaa	gataacctagt	tattcagggt
3001	gatgatcgta	tgaagcttcc	cagtccaaat	gacagcaagt	tctttcagaa	tctcttggat
3061	gaagaggatt	tggaaagatat	gatggatgct	gaggagtact	tgggtccctca	ggctttcaac
3121	atcccacctc	ccatctatac	ttccagagca	agaattgact	cgaataggag	tgaatttgga
3181	cacagccctc	ctcctgccta	cacccccatg	tcaggaaacc	agtttgtata	ccgagatgga
3241	ggtttttgctg	ctgaacaagg	agtgtctgtg	ccctacagag	ccccaaactag	cacaattcca
3301	gaagctcctg	tggcacaggg	tgctactgct	gagatttttg	atgactcctg	ctgtaattggc
3361	accctacgea	agccagtggc	accccatgtc	caagaggaca	gtagcaccca	gaggtacagt
3421	gctgacccca	ccgtgtttgc	cccagaacgg	agcccacgag	gagagctgga	tgaggaaggt
3481	tacatgactc	ctatgcgaga	caaaccctaaa	caagaatacc	tgaatccagt	ggaggagaac



FIGURE 1B

3541 ccttttgttt ctccggagaaa aaatggagac cttcaagcat tggataatcc cgaatatcac
3601 aatgcatcca atgggtccacc caaggccgag gatgagtatg tgaatgagcc actgtacctc
3661 aacacctttg ccaacacctt gggaaaagct gactaccta gaacaacat actgtcaatg
3721 ccagagaagg ccaagaaagc gtttgacaac cctgactact ggaaccacag cctgccacct
3781 cggagcacc ctcagcacc agactacctg caggagtaca gcacaaaata tttttataaa
3841 cagaatgggc ggatccggcc tattgtggca gagaatcctg aatacctctc tgagttctcc
3901 ctgaagccag gcactgtgct gccgcctcca ccttacagac accggaatac tgtggtgtaa
3961 gctcagttgt ggttttttag gtggagagac acacctgctc caatttcccc accccctct
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4381 tgatgtgtgc atatttagca tccctggaaa tcataataaa gtttccatta gaacaaaaga
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4501 cagtttctgt cctagcaagt aagaatggcc aactcaactt tcataattta aaaatctcca
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